

Severe Paediatric Asthma Collaborative in Europe (SPACE) protocol for a European registry

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Take home message: An ERS funded CRC has developed a protocol for a paediatric severe asthma study to support asthma biologics trials.

Author Contributions: F.Rusconi and J.Grigg are joint Chief Investigators and principal applicants for this CRC project. R.M Fernandes, B. Karadag, M.W.H Pijnenburg and F. Rusconi performed the literature review for registry entry criteria. J.D. Chalmers facilitated the liaison with HIC at University of Dundee. All other authors contributed equally to the design and implementation of the registry.

Abstract

The development of new asthma biologics and receptor blockers for the treatment of paediatric severe asthma raises challenges. It is unclear whether there are sufficient children in Europe to recruit into randomised placebo-controlled trials to establish efficacy and safety in this age group.

In February 2016, the European Respiratory Society funded a clinical research collaboration entitled “Severe Paediatric Asthma Collaborative in Europe” (SPACE). We now report the SPACE protocol for a prospective pan-European observational study of paediatric severe asthma. Inclusion criteria are 1) age 6-17 years, 2) severe asthma managed at a specialised centre for ≥ 6 months, 3) clinical and spirometry evidence of asthma, and 4) reaching pre-defined treatment threshold. Exclusion criterion is the presence of conditions which mimic asthma symptoms. Eligible children will be prospectively recruited into a registry, recording demographics, comorbidities, quality of life, family history, neonatal history, smoking history, asthma background, investigations, and treatment. Follow-up will provide longitudinal data on asthma control and treatments changes.

The SPACE registry, by identifying well-phenotyped children eligible for clinical trials, and the amount of overlap in eligibility criteria, will inform the design of European trials in paediatric severe asthma, and facilitate observational research where data from single centres are limited.

Introduction

In order to deliver new treatments to children and adolescents with severe asthma, clinical trials of new biologics and receptor blockers are needed, since data on safety and efficacy from trials in adults cannot always be appropriately extrapolated to this age group. There are however problems with performing clinical trials in children and adolescents with asthma. For example, severe asthma phenotypes are less well characterised, severity of paediatric asthma tends to vary greatly, numbers are fewer than in adult asthma, long-term adverse effects may be more important, and children and adolescents often engage less well with complex clinical trial interventions than adults [1]. Indeed, it is currently unclear whether the subphenotypes and putative endotypes of asthma eligible for some of the new monoclonal treatments even exist in children with severe asthma and whether there are sufficient children to support multiple trials in Europe with overlapping eligibility criteria. In 2015, the European Medicines Agency (EMA) expressed their view to officers of the Paediatric Assembly of the European Respiratory Society (ERS), that recruitment of children with asthma into trials of new biologics would be significantly enhanced if there were a network of European respiratory paediatricians able to both support recruitment and provide academic advice and guidance to the EMA and industry. In 2015, the ERS funded a clinical research collaboration (CRC), developed by members of its Paediatric Assembly (Assembly 7) to develop the evidence and structures to enable European paediatricians to identify and recruit eligible children. Funding of CRC's is a major route whereby the ERS engages in the promotion and coordination of activities in respiratory medicine by working to advance science and clinical research within a specific disease area (<https://www.ersnet.org/research/clinical-research-collaborations>). The aim of this CRC entitled "Severe Paediatric Asthma Collaborative in Europe" (SPACE) is to; i) develop a minimum "core" eligibility criteria dataset which will identify children and adolescents with

genuine severe asthma as per ERS/ATS taskforce guidelines, by using this dataset, prospectively survey the number of children eligible for current and proposed trials, ii) develop a bid for a registry of eligible children to not only enhance participation in trials but also generate new insights into responsive subgroups, and iii) actively engage with children and adolescents to help understand how to better promote trial opportunities and remove barriers to involvement in therapeutic clinical trials of new severe asthma treatments. We now report the protocol for the SPACE registry, an open, pan-European registry of paediatric patients with severe asthma.

Study Objectives

The objectives of SPACE are:

- To develop a pan-European multi-centred, prospective and observational registry of children with severe asthma, incorporating baseline and annual follow-up data.
- To agree upon common definitions and registry entry criteria across Europe. The registry will record the demographics, co-morbidities, aetiology, treatment, resource use, exacerbations, severity and prognosis of severe paediatric asthma across Europe; providing a comprehensive real-life description of characteristics and burden of severe paediatric asthma across Europe.
- To provide a database of well-phenotyped paediatric patients with true severe asthma and to develop an infrastructure to support trials of new therapies in paediatric asthma (especially biologics), aimed at increasing participation of European children in these trials, enhancing participation of ERS paediatricians, children with severe asthma and their families in the planning of future studies, and generating new academic insights into target populations.

Protocol development

The SPACE registry is based on the successful ERS CRC for Bronchiectasis (EMBARC), a registry supported by the Health Informatics Centre (HIC) at the University of Dundee [2].

With their support and close liaison, the SPACE protocol was developed following thorough discussions amongst leading respiratory paediatricians from Germany, Italy, the Netherlands, Norway, Portugal, Turkey, and the UK.

The CRC first set up a core group to systematically review the literature on proposed definitions of severe paediatric asthma (details on the methods of the systematic review will be reported separately). Based on the pre-selected variables and eligibility criteria, a prototype of the registry was developed.

Registry

The SPACE registry will be a prospective, non-interventional, observational cohort study, with a short-term target of enrolling 7-20 patients per centre over the course of the first year. Enrolment is planned to increase with time and future funding. Study centres will be invited to participate on the basis of ability to include patients from a severe asthma clinic or service, and a track record of contributing to clinical research. Consideration will be given to encourage investigators from under-represented parts of Europe (such as Eastern Europe) to contribute, making this a representative and truly pan-European registry.

Asthma management will be according to local policies with no additional intervention from the study. The registry will thereby identify differences in practice in various European countries. Children and their parents will provide assent and consent for data collection at enrolment (detailed below) and follow-up, in line with local regulations.

Local principle investigators will be practising Paediatric Respiratory Consultants in tertiary or specialised units. The initial phase is planned as a 1-year prospective survey including recruitment and data collection. This will generate data for the first cross-sectional analysis. Should future funding allow, prospective data will be collected with a follow-up phase which will comprise of annual follow-ups. This will provide longitudinal data on any changes in asthma control and treatments. Enrolment and number of participating centres and countries may also expand. We designed the ethics approval (detailed below) to include any future expansion.

Participants

Eligible participants are identified using the inclusion and exclusion criteria (tables 1 and 2).

Recruitment of children

Parents and children will be invited to participate in the registry during routine clinical encounters and will be screened for eligibility using the inclusion and exclusion criteria defined above. If patients are eligible, they and their parents will be provided with a copy of the patient information sheet and parent information sheet which will provide details of the registry aims and the type of clinical information collected. Children and their parents will be

asked to provide written informed assent and consent following ample time to consider participation.

Participants and their parents will be informed and will be required to agree to their medical records being inspected by the investigators or their delegate, if required, but understand that their confidential details will not be disclosed outside the research team, as non-identifiable data will be stored within the database. The participant will receive a copy of the consent and assent forms and a copy will be filed in their medical notes.

Data collection

Data will be collected on two or more occasions: *Case report form* – the baseline dataset at enrolment, incorporating all relevant paediatric severe asthma variables. *Annual review form* – if funding allows, follow-up data collected annually (\pm 3 months), signifying changes in medications, exacerbations, hospital admissions and survival status.

The dataset is sufficiently simple that any specialist asthma clinic will be able to provide the data. Nevertheless, the data are sufficiently robust that they will provide a comprehensive overview of all aspects of paediatric severe asthma care in Europe. The data fields were established following consultation with European stakeholders. There will be an option for participants to consent for future contact concerning participation in future clinical studies. The network will therefore aid research collaborations around Europe. Figure 1 shows part of the online data collection platform.

An adherence assessment along with data on comorbidities, risk factors for asthma, family history, neonatal history and smoking history will be recorded. The Paediatric Asthma

Quality of Life Questionnaire (PAQLQ) score will be incorporated into the registry.

Asthma background information

Lung function

Best and worst pre- and post-bronchodilator spirometry results in the last 6 months will be recorded. Spirometry will be performed according to the American Thoracic Society/ERS standards [3]. The GLI-2012 equations will be used to generate predicted values, lower limits of normal and z-scores for spirometric indices.

Results of bronchial provocation test, if applicable, may be recorded.

Asthma investigations

Most recent results of exhaled fractional nitric oxide (FeNO), sputum and blood eosinophil counts, total IgE, specific IgE, and skin prick test, radiology and bronchoscopy findings including bronchoalveolar lavage cytology and microbiology are recorded, if available.

Asthma control

Asthma control will be assessed by ACQ and/or ACT scores within 4 weeks of enrolment, along with GINA assessment. Number of exacerbations (episodes requiring systemic steroids), hospital admissions, non-invasive or ventilatory support in the last 12 months will be documented. Number of total ICU admissions and mechanical ventilation since the diagnosis of asthma will also be recorded.

Treatment

Details on various inhaled and oral therapies (bronchodilators, steroids,

anticholinergic, leukotriene receptor antagonist, antihistamines, anti-reflux medications, theophylline, antibiotics and monoclonal antibody) will be recorded. Further details on monoclonal antibody including previous assessment, usage and reasons for discontinuation will be documented. Any adverse effect of chronic steroid use will also be noted. Treatment options will be regularly updated as new treatments become available during the study.

Ethics, governance, data access and quality control

This study received ethical approval from the London (Bloomsbury) Research Ethics Committee in the UK on 20/02/2018 (18/LO/0178). The registry was developed according to the recommendations by the EPIRARE (European Platform for Rare Disease Registries) consortium (http://www.epirare.eu/_down/del/D4_GuidelinesfordatasourcesandqualityforRDRegistriesinEurope.pdf) and EUCERD on registries in the European Union (http://www.eucerd.eu/?post_type=document&p=1218).

The registry is secured at the Health Informatics Centre (HIC) at the University of Dundee. The Safe Haven model (<http://www.scot-ship-toolkit.org.uk/information-page/ship-safe-havens>) will provide anonymous registry data to researchers throughout Europe. The Safe Haven is a virtual desktop allowing for data access and analysis securely – data security is ensured by inhibition of data copying or downloading. Local data access will be unrestricted to active investigators and other stakeholders. The joint Chief Investigators and the Steering Committee have a download facility to enable quality check and data review. Missing data will be highlighted to the investigators and random audit will be conducted at study sites.

Annual summaries of the study may be presented at conferences or used for clinical or scientific publications.

Requests to access or analyse the database will be submitted to the SPACE Scientific Committee.

The HIC database and governance processes surrounding data management and access are fully compliant with the UK Data Protection Act 1998 and the Data Protection Directive 95/46/EC of the European Parliament and of the Council (1995), and will also comply with the new EU General Data Protection Regulation from May 2018. Data sharing agreements will be established between sites and the HIC, warranting compliance with national laws on ethics and data protection.

The study will be conducted in line with Good Clinical Practice. A favourable ethical opinion will be obtained, if applicable, by each site from the appropriate research ethics committee or institutional review board. All patients, or their parents for those under the age of 16, must provide written informed consent prior to participation.

Patient involvement

The European Lung Foundation (ELF) (www.europeanlung.org) is working with SPACE network to ensure appropriate patients consultation across Europe. The registry and relevant documents were developed with the review and feedback from the patient advisory group (PAG). Members of the ELF and PAG form part of the Steering Committee of the SPACE registry. With the help of ELF, patient information resources in multiple languages will be established.

Discussion

The proposed protocol has strengths and limitations. Its strengths are; 1) the wide range of participating specialised centres across Europe (table 3), with the capacity to provide a good representation of well-phenotyped children for future pan-European studies, 2) its close link with the ERS CRC EMBARC, which has proven to be a successful international registry and serves as a guidance for the development of SPACE, 3) participation of industrial representatives (from GlaxoSmithKline and AstraZenca via previous links with CRC members) who provide advice on the development of this registry, and are the industry links for the development of clinical trials, and 4) its link with patient organisations, the supporting documents for the registry were developed with the support of ELF and their PAG which consists of adult patients who have had severe asthma from a young age and parents of children with severe asthma. The registry's limitations are that 1) the initial cross-sectional data analysis is not reflective of all major European centres managing severe asthma, 2) the lack of paediatric patient representatives and limited representation from outside northern Europe, 3) no current direct industry funding, and 4) no long term funding. Future work of SPACE will both address these limitations, and develop an analysis plan of data from the initial cross-sectional data collection.

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Legend for Figures

Figure 1. The Severe Paediatric Asthma Collaborative in Europe (SPACE) data collection platform.

References

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Table 1. Inclusion and exclusion criteria for SPACE registry participants

Inclusion criteria	Exclusion criteria
Age 6-17 years	Patient's symptoms are primarily due to the following conditions, which might mimic asthma: <ul style="list-style-type: none"> • Allergic Bronchopulmonary Aspergillosis • Bronchiolitis Obliterans • Cystic Fibrosis • Primary Ciliary Dyskinesia • Significant bronchiectasis (not related to asthma) • Severe Immunodeficiency/ Immunosuppression • Central airway obstruction, or compression • Congenital airway malformation (e.g. vascular ring) • Foreign body • Tracheobronchomalacia • Interstitial Lung Disease • Lobectomy • Other pulmonary surgery • Carcinoid or other tumour • Congenital Heart Disease • Connective Tissue Disease • Neuromuscular Diseases
Diagnosis confirmed, evaluated and managed at a specialised centre ≥ 6 months	
Symptoms: <ul style="list-style-type: none"> • Wheeze heard by trained healthcare professional <u>OR</u> • Self-reported wheeze in last 12 months 	
Spirometry evidence of asthma: <ul style="list-style-type: none"> • Bronchial obstruction with bronchodilator reversibility $\geq 12\%$, <u>OR</u> • Bronchial provocation test with $\geq 10\%$ fall in FEV₁ 	
Treatment: <ul style="list-style-type: none"> • High dose inhaled corticosteroids (table 2) for ≥ 6 months + Long acting beta-agonist / Leukotriene modifier <u>OR</u> • Systemic corticosteroids for $\geq 25\%$ of last 12 months 	

Table 2. Definition of high dose inhaled corticosteroid for inclusion criteria

Inhaled Corticosteroid	Dose (µg)	Inhaler type
Beclomethasone	≥800 ≥320	DPI, CFC MDI HFA MDI
Budesonide	≥800	MDI, DPI
Ciclesonide	≥160	HFA MDI
Fluticasone	≥500	HFA MDI, DPI
Fluticasone furoate	≥200	DPI
Fluticasone propionate	≥400 ≥500	DPI HFA
Mometasone	≥500	DPI
Triamcinolone	≥1200	-

DPI = Dry Powder Inhaler
MDI = Metered-Dose Inhaler
CFC = Chlorofluorocarbon
HFA = Hydrofluoroalkane

Table 3. Participating specialised centres across Europe

Participating Centres	Country
Marien Hospital	Germany
Anna Meyer Children's University Hospital	Italy
Sapienza University of Rome	Italy
Emma Childrens Hospital AMC	The Netherlands
Erasmus MC-Sophia Children's Hospital	The Netherlands
Oslo University Hospital	Norway
Hospital de Santa Maria	Portugal
Marmara University Faculty of Medicine Pendik Hospital	Turkey
Royal Brompton Hospital	UK
Royal Hospital for Sick Children, Edinburgh	UK
Royal London Hospital	UK